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(54) Title: TRANSGENIC ANIMALS FOR ANALYSING CYP3A4 CYTOCHROME P450 GENE REGULATION

(57) Abstract: The invention relates to the generation of non-human transgenic animals comprising a reporter construct for producing a detectable amount of a reporter molecule operably linked to a transcriptional regulatory nucleic acid molecule from the human CYP3A4 gene located between the initiation of transcription site of the gene and a position located 13,000 nucleotides upstream from the site. The invention also relates to the use of these animals for determining the effect of a compound, particularly, but not exclusively, a xenobiotic or steriod, on the regulation of expression of the CYP3A4 gene in a human.

TRANSGENIC ANIMALS FOR ANALYSING CYP3A4 CYTOCHROME P450 GENE REGULATION

TECHNICAL FIELD OF THE INVENTION

The invention relates to the generation of a transgenic animal and to the use of the animal for determining the effect of a compound, particularly, but not exclusively, a xenobiotic or steroid, on the regulation of expression of a P450 gene in a human.

BACKGROUND OF THE INVENTION

Many endogenous and exogenous compounds are observed to have a therapeutic effect in drug development trials *in vitro*. However, the intended therapeutic effect is often not realised in clinical practice, for example, when compounds are co-administered, because certain compounds induce the expression of the CYP3A4 gene. This induction generates CYP3A4 cytochrome P450 molecules which metabolise compounds before the intended therapeutic effect of each compound can be realised. Accordingly, induction of expression of the CYP3A4 gene interferes with intended dosage, leading to therapeutic failure or sub-optimal treatment.

Induction of CYP3A4 gene expression is a significant problem for drug development because time, resources and expense are wasted in the development of candidate drugs for therapy of particular disease conditions which will ultimately fail or perform sub-optimally in clinical practice.

It would be advantageous to have an animal model for use in drug development trials from which, at an early stage of drug development, one could determine whether a

candidate drug would be likely to achieve an intended therapeutic effect in a human.

Such an animal model would not be useful unless at least some of the aspects of the regulation of CYP3A4 gene expression in the human, especially tissue specific expression, are reproduced. This is because in the human, the CYP3A4 gene is expressed in specific tissues, including liver and small intestine, which many compounds inevitably come into contact with when administered for the purpose of therapy. Accordingly, one would be unable to determine whether the bio-availability of a candidate drug would be sufficient for achieving an intended therapeutic effect in clinical practice in a model which does not reproduce the constitutive and xenobiotic induced tissue specific expression of the CYP3A4 gene that is observed in the human.

WO99/61622 and Goodwin et al. 1999 disclose a nucleic acid molecule located 8 kb upstream from the initiation of transcription site of the CYP3A4 gene which regulates transcription of the CYP3A4 gene in response to xenobiotic compounds. These documents do not disclose elements for regulating the constitutive and xenobiotic inducible tissue specific and developmental expression of the CYP3A4 gene observed in a human.

There is a need for an animal model which reproduces at least some aspects of the expression of the CYP3A4 gene in a human, for determining whether a compound, for example, one identified in a drug development trial, would be likely to induce CYP3A4, and hence cause drug-drug interactions, or auto-induction of the metabolism of the drug under study.

DESCRIPTION OF THE INVENTION

The invention seeks to address the above identified need and in a first aspect provides a non-human mammal comprising:

(a) a regulatory nucleic acid molecule which is capable of regulating transcription of the human CYP3A4 gene and which comprises a nucleotide sequence that is identical to a sequence of the human CYP3A4 gene located between the initiation of transcription site of the gene and a position located at least 13,000 nucleotides upstream from the site; and

(b) a reporter nucleic acid molecule for producing a detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule

wherein the reporter and regulatory nucleic acid molecules are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

As described herein, the inventors have found that the incorporation of a region of the human CYP3A4 gene that is located between the initiation of transcription site of the gene and a position 13,000 nucleotides upstream of the initiation of transcription site into an animal model provides the animal with sufficient genetic information for reproducing the constitutive and xenobiotic induced tissue specific expression of the CYP3A4 gene that is observed in humans. More specifically, the inventors have generated animal models which contain a transgene comprising this region and have observed that these models provide constitutive and xenobiotic inducible expression of a transgene in a tissue pattern which reproduces the

tissue specific expression of CYP3A4 which is observed in a human. Importantly, the level of constitutive expression is sufficient to allow one to observe the effect on the regulation of tissue specific transgene expression, of administration of a compound, for example, a xenobiotic or steroid, to the animal.

Further, the inventors have observed that the animal models described herein also reproduce aspects of the constitutive and xenobiotic inducible developmental expression of the CYP3A4 gene that is observed in humans.

These findings are unanticipated because prior to the invention, there was no suggestion that the genetic information required for simulating the constitutive and xenobiotic induced tissue specific or developmental expression of the CYP3A4 gene that is observed in a human would be contained in the region of the human CYP3A4 gene between the initiation of transcription site of the gene and a position 13,000 nucleotides upstream of the initiation of transcription site.

Further, prior to the invention, differences in the induction profile of the mouse CYP3A11 and the human CYP3A4 gene had been observed, and differences had also been observed in the ligand binding profile of mouse transcription factors, especially PXR and CAR, and human PXR and CAR. Accordingly, there was no suggestion that a non-human animal would have factors sufficient for interacting with a region of the CYP3A4 gene for reproducing the constitutive and xenobiotic induced tissue specific or developmental expression of CYP3A4 observed in a human.

Further, prior to the invention, mechanisms associated with transgene integration had been observed, such as gene

silencing and mosaic transgene expression which limited the extent to which an a transcriptional enhancer element incorporated into a trangenic model could reproduce regulation of gene expression observed in a human. Accordingly, there was no suggestion that a region of the human CYP3A4 gene would be capable of reproducing the regulation of expression of the CYP3A4 gene that is observed in a human. However, as described herein, the inventors have shown in 2 separate founder lines that the expression of the transgene reproduces aspects of CYP3A4 gene expression that are observed in humans.

Thus in a second aspect, the invention provides a non human mammal comprising:

(a) a regulatory nucleic acid molecule comprising a nucleotide sequence that is identical to the nucleotide sequence of the human CYP3A4 gene that extends about 13,000 nucleotides upstream from the initiation of transcription site of the gene; and

(b) a reporter nucleic acid molecule for producing a detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule

wherein the reporter and regulatory nucleic acid molecules are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

In one embodiment, the regulatory nucleic acid molecule comprises the sequence shown in SEQ ID NO:1.

Further, as described herein, the inventors have generated transgenic animals which contain a region of the human

CYP3A4 gene between the initiation of transcription site and a position about 3,200 nucleotides upstream of the initiation transcription site and observed that the transgene is not constitutively expressed or inducible by xenobiotics in these animals. Accordingly, the inventors have found that the genetic information required for reproducing the constitutive and xenobiotic induced tissue specific and developmental expression of CYP3A4 observed in a human is contained in the region of the human CYP3A4 gene between the position located about 3,200 nucleotides upstream of the initiation of transcription site of the gene and a position 13,000 nucleotides upstream of the initiation of transcription site.

Thus, in a third aspect, the invention provides a non-human mammal comprising:

(a) a regulatory nucleic acid molecule comprising a nucleotide sequence that is identical to the sequence of the human CYP3A4 gene that extends about 8,000 nucleotides upstream from a position about 3,000 nucleotides upstream from the initiation of transcription site of the gene; and

(b) a reporter nucleic acid molecule for producing a detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule

wherein the reporter and regulatory nucleic acid molecules are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

In one embodiment, the regulatory nucleic acid molecule comprises the sequence shown in SEQ ID NO:2.

In a fourth aspect, the invention provides a non-human mammal comprising:

(a) a regulatory nucleic acid molecule which is capable of regulating transcription of the human CYP3A4 gene and which comprises a nucleotide sequence that is identical to the sequence of the human CYP3A4 gene that extends about 600 nucleotides upstream from a position about 7,200 nucleotides upstream of the initiation of transcription site of the gene; and

(b) a reporter nucleic acid molecule for producing a detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule

wherein the reporter and regulatory nucleic acid molecules are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

In one embodiment, the regulatory nucleic acid molecule comprises the sequence shown in SEQ ID NO:3.

In another embodiment, the regulatory nucleic acid molecule has the sequence of any one of the following fragments of the CYP3A4 gene:
(i) a fragment consisting of from nucleotide positions -13,000 to +53;
(ii) a fragment consisting of from nucleotide positions -13,000 to -12,700 contiguous with -8000 to +53;
(iii) a fragment consisting of from nucleotide positions -13,000 to -5,100 contiguous with -1,200 to +53;
(v) a fragment consisting of from nucleotide positions -7,800 to -6,000 contiguous with -362 to +53;
(vi) a fragment consisting of from nucleotide positions

-7,500 to -6,000 contiguous with -362 to +53;

A regulatory nucleic acid molecule which has the sequence of a fragment consisting of from nucleotide positions -7836 to -7207 contiguous with -362 to +53 is particularly preferred, as this construct contains the minimal sequences necessary for regulating transcription of the human CYP3A4 gene, more specifically, an element responsive to xenobiotics (the "Xenobiotic Response Element Module" or "XREM") and the proximal promoter of the CYP3A4 gene.

The regulatory nucleic acid molecule of the invention typically contains at least one enhancer capable of regulating transcription of a human CYP3A4 gene when contacted with a nuclear receptor. Examples of such enhancers are those capable of regulating transcription of a human CYP3A4 gene when contacted with a nuclear receptor bound to a ligand, such as a xenobiotic or steroid. Other examples are those capable of regulating transcription of a human CYP3A4 gene when contacted with a nuclear receptor consisting of a heterodimer of PXR (pregnane X receptor, otherwise known as SXR (steroid and xenobiotic receptor)) and RXR (9-cis retinoic acid receptor), or CAR (constitutive androstane receptor-β) and RXR.

The inventors believe that certain nucleic acid molecules which have substantially the same nucleotide sequence as a regulatory nucleic acid molecule of the invention would also have sufficient genetic information for reproducing the constitutive and xenobiotic induced tissue specific and developmental expression of the CYP3A4 gene that is observed in a human. Accordingly, it will be understood that nucleotides could be modified or deleted in regions of the regulatory nucleic acid molecule, more specifically, those regions which do not contain an

enhancer such as those described above, without significantly limiting the capacity of the molecule to regulate transcription of the human CYP3A4 gene.

The inventors recognise that it would be advantageous to provide an animal model further capable of reproducing the expression of other human genes, specifically those genes encoding products which modify or modulate the therapeutic activity of exogenous and endogenous compounds used for therapy and cause drug-drug interactions, for example, cytochrome P450 genes or ABC transporter superfamily genes, for example, P-glycoprotein (otherwise known as MDR-1). The regions controlling the constitutive and xenobiotic induced tissue specific expression of some of these genes are known, and in some instances, non-human animal models have been generated. The inventors recognise that the genetic background of these animals could be incorporated into the non-human mammal of the present invention, for example, by conventional breeding techniques.

Thus in a fifth aspect, the invention provides a non-human mammal of any one of the first to fourth aspects of the invention, further comprising:

(c) a further regulatory nucleic acid molecule which is capable of regulating transcription of a human gene; and

(d) a further reporter nucleic acid molecule for producing a detectable amount of a further reporter molecule for indicating regulation of transcription of the further reporter nucleic acid molecule by the further regulatory nucleic acid molecule

wherein the further reporter and further regulatory nucleic acid molecules are arranged to permit the further

regulatory nucleic acid molecule to regulate transcription of the further reporter nucleic acid molecule.

In one embodiment, the at least one further regulatory nucleic acid molecule has a sequence shown in SEQ ID NO:4. In another embodiment, the at least one further regulatory nucleic acid molecule has a sequence shown in SEQ ID NO:5.

Although the regulatory nucleic acid molecule of the invention described herein is sufficient for reproducing the constitutive tissue specific and developmental expression of the CYP3A4 gene that is observed in a human, the inventors recognise that aspects of the xenobiotic inducibility of the gene could be better reproduced in an animal by incorporating at least one human transcription factor that is capable of interacting with the regulatory nucleic acid molecule for regulating transcription of the human CYP3A4 gene. Examples of such factors are nuclear receptors. These receptors may be those capable of regulating CYP3A4 gene transcription in a human when the receptor is bound to a ligand, such as a xenobiotic or steroid. One example of such a receptor is the human PXR (pregnane X receptor, otherwise known as SXR (steroid and xenobiotic receptor)). Another suitable receptor is the human CAR (constitutive androstane receptor-β). Non-human animals comprising a human PXR or CAR receptor are known. The inventors recognise that the genetic background of these animals could be incorporated into the non-human mammal of the present invention, for example, by conventional breeding techniques.

Thus in a sixth aspect, the non-human animal of the invention further comprises at least one human transcription factor for regulating transcription of a human CYP3A4 gene. Preferably the transcription factor is a nuclear receptor. Preferably, the nuclear receptor is a

heterodimer of the human PXR (pregnane X receptor, otherwise known as SXR (steroid and xenobiotic receptor)) and human RXR (9-cis retinoic acid receptor) or human CAR (constitutive androstane receptor-β) and human RXR.

It follows that the reporter nucleic acid molecule can be any molecule which is capable of detection when the reporter nucleic acid molecule is transcribed. For example, the reporter nucleic acid molecule could be the CYP3A4 cytochrome, or the mRNA transcript which is translated to produce the cytochrome. Those reporter molecules which are commercially available, including firefly luciferase, β- galactosidase, alkaline phosphatase, green fluorescent protein or chloramphenicol acetyl transferase can be used.

Thus in one embodiment, the reporter nucleic acid molecule is capable of producing a reporter molecule selected from the group of reporter molecules consisting of firefly luciferase, β-galactosidase, alkaline phosphatase, green fluorescent protein or chloramphenicol acetyl transferase.

While the non-human mammal of the invention, as exemplified below, is a mouse, the inventors believe that any other non-human mammal could be used in the invention, especially those for which standard transgenic techniques have been developed including for example, rat and rabbit. However, typically the non-human mammal is a mouse.

In another aspect, the invention provides a tissue of a non-human mammal of the invention.

In one embodiment, the tissue is an embryo capable of producing a non-human mammal of the invention.

In a further aspect, the invention provides a method of determining whether a compound is capable of effecting the transcription of a human CYP3A4 gene the method comprising the following steps:

(a) administering the compound to a non human mammal according to the invention and
(b) determining whether the reporter molecule is produced by the reporter nucleic acid molecule in the mammal.

In one embodiment, the production of the reporter molecule indicates that the binding compound is capable of effecting the transcription of the human CYP3A4 gene.

Any compound can be tested in the method however, preferred compounds are xenobiotic or steroid compounds.

The inventors recognise that a non human animal which comprises a 5′ flanking region of CYP3A4 gene but which is deficient for the region from -7836 to -7207 would be useful as a negative control in a method for determining whether a compound is capable of regulating transcription of the human CYP3A4 gene.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. CYP3A4/*lacZ* transgene constructs used to generate transgenic mice. The upstream regions of the human *CYP3A4* gene are depicted as open boxes with the position of the XREM at approximately -7.5kb of the CYP3A4 gene indicated by cross-hatching. The 5′-flanking region extended from 56bp downstream of the transcription initiation site to a HindIII site at -3,213 in the construct designated -3CYP3A4/*lacZ* and to a KpnI site at -12,926 kb in construct

-13CYP3A4/lacZ. The coding region of the E.coli *lacZ* gene together with eukaryotic translational initiation and termination signals, transcription termination and poly adenylation sites are indicated by a solid box.

Figure 2. Xenobiotic induction of hepatic transgene expression. Female mice from line 9/4 harbouring the -13CYP3A4/*lacZ* transgene were treated with various reagents. Histochemical staining of liver slices with X-gal revealed an increased zone of blue staining cells containing β-galactosidase after treatment with rifampicin, phenobarbital and pregnenolone 16α-carbonitrile compared with corn oil treated mice.

Figure 3. Comparison of the xenobiotic induction profile of the -13CYP3A4/*lacZ* transgene with the mouse Cyp3a11 gene. Transgenic mice from line 9/4 were treated with a range of xenobiotic reagents and naturally occurring steroids. **A.** Transgene expression was assessed by determining β-galactosidase activity in total liver lysates using the ONPG assay. The units of β-galactosidase activity are given as A_{420}/mg liver/minute. Dexamethasone and pregnenolone 16α-carbonitrile were the most potent xenobiotic activators of the -13CYP3A4/*lacZ* transgene, while rifampicin treatment resulted in relatively low levels. The steroids pregnenolone and 17α-progesterone were very weak inducers. **B.** Hepatic expression of the endogenous mouse Cyp3a11 gene was examined in the same mice by Northern analysis. A similar pattern of induction to the CYP3A4/*lacZ* transgene was observed with both xenobiotic and endogenous regulators. The data are presented as the mean +/- the standard deviation for 3 animals.

Figure 4. Dose response of -13CYP3A4/*lacZ* transgene expression after treatment with dexamethasone. **A.** Male mice from line 9/4 were treated with from 1 to 100mg/kg dexamethasone. Higher doses of dexamethasone resulted in increased β-galactosidase activity (determined in liver lysates as described in Fig. 3).**B.** Zonal expansion of transgene expression with increasing doses of dexamethasone. X-gal staining of frozen liver sections revealed greater numbers of hepatocytes containing transgene-derived β-galactosidase activity after treatment with 1, 10 and 100 mg/kg dexamethasone. At low doses there are limited numbers of transgene -expressing cells immediately adjacent to the central vein. With higher doses there are more cells committed to transgene expression extending across the liver lobule towards the portal tract.

Figure 5. (SEQ ID NO:1) Sequence of the CYP3A4 5'-flanking region included in the -13 CYP3A4/lacZ construct. This sequence corresponds to -12,926 to +56 base pairs relative to the transcription initiation site of the CYP3A4 gene.

Figure 6. (SEQ ID NO:2)Sequence of the 5'-flanking region of the CYP3A4 gene extending from -12,926 to -3,213 base pairs and representing the difference in sequence between the -13 CYP3A4/lacZ and the -3 CYP3A4/lacZ constructs.

Figure 7. (SEQ ID NO:3)The "Xenobiotic-Responsive Enhancer Module" (XREM) of the human CYP3A4 gene. This region encompasses -7836 to -7207 base pairs relative to the transcription initiation site of the CYP3A4 gene.

Figure 8. (SEQ ID NO:4)The 5'-flanking region of the human CYP3A7 gene (Genbank Accession No. AF329900). The extent of the sequences is -11,133 to +52 base relative to the transcription initiation site of the CYP3A7 gene.

Figure 9. (SEQ ID NO:5)Sequence of the 5'-flanking region of the human MDR1 gene (p-glycoprotein gene) encompassing -10,000 to +200 base pairs relative to the transcription initiation site of the MDR1 gene. Sequence derived from within Genbank sequence Accession Number AC002457.

An embodiment of the invention is now described in the following Example which will be understood to merely exemplify and not to limit the scope of the invention.

EXAMPLE

MATERIALS AND METHODS

Transgene constructs. Two transgene constructs were synthesized with the upstream 5' flank of the human cytochrome P450 *CYP3A4* gene linked to the E. coli *lacZ* reporter gene (Figure 1). The first construct, designated -3CYP3A4/*lacZ*, contained the region of the *CYP3A4* gene from the HindIII site at -3213bp relative to the transcription start site to nucleotide +56bp downstream of the transcription start site. The other construct, designated -13CYP3A4/*lacZ*, included the region of the CYP3A4 gene from the KpnI site at -12,926bp upstream to +56bp downstream of the transcription start site. It includes the DNA sequences of the XREM region located between -7836 and -7208 in addition to the proximal promoter of the *CYP3A4* gene. The DNA sequence of the *CYP3A4* gene between -10468bp and +906bp has been determined and deposited with the

GenBank/EMBL/DDJB database under accession number AF185589. Additional sequence information covering the region -10,469bp to -12,926bp was obtained from publically accessible Genbank files. The E.coli *lacZ* reporter gene comprises the coding region for the bacterial enzyme β-galactosidase flanked by DNA sequences for eukaryotic translational start and stop signals, SV40 transcriptional termination and polyadenylation signals and an intron. The *CYP3A4/lacZ* transgene constructs were released from vector sequences and purified on agarose gels prior to microinjection

Generation of transgenic mouse lines. Mice carrying the CYP3A4/*lacZ* transgenes were created by microinjection of the DNA constructs into the pro-nuclei of zygotes harvested from FVB/N strain mice. Microinjection and manipulation of embryos were carried by standard techniques. Stable transgenic mouse lines were established by breeding from transgenic founders identified by Southern analysis.

Administration of xenobiotics to mice. 8-10 week old male and female mice hemizygous for the -3CYP3A4/*lacZ* and -13CYP3A4/*lacZ* transgenes were used to test the ability of a range of xenobiotics and hormones to activate expression of transgene-derived β-galactosidase. Mice were administered the following reagents and vehicles by single daily intraperitoneal injection for 4 days: rifampicin/corn oil; dexamethasone phosphate/H_2O; pregnenolone 16α-carbonitrile/2% Tween 20 in H_2O; phenobarbital/H_2O; clotrimazole/2% Tween 20; phenytoin/2% Tween 20; 17α-OH progesterone/2% Tween 20; pregnenolone/2% Tween 20. All reagents were supplied by Sigma Chemical Co. (St Louis, MO) except for dexamethasone phosphate which was obtained from Faulding (Mulgrave, Australia) and pregnenolone 16α-

carbonitrile from Upjohn Co. (Kalamazoo, MI). The dose used for all reagents to test for induction of the transgene was 100mg/kg body weight. Dose response studies were carried out in the range of 1-100mg/kg with male hemizygous transgenic mice.

Analysis of transgene and mouse Cyp3a gene expression. β-galactosidase activity was visualised in slices and frozen sections of liver and other tissues by staining with X-gal (5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside). Tissues were fixed in 0.25% glutaraldehyde, 0.1M phosphate buffer pH7.3, 5mM EGTA, 2 mM $MgCl_2$: washed in 0.1M phosphate buffer pH7.3, 0.01%sodium deoxycholate, 0.025% NP40, 2mM $MgCl_2$ and stained by incubation at 37°C in wash solution supplemented with 1mg/ml X-gal, 5mM potassium ferricyanide, and 5mM potassium ferrocyanide. The level of β-galactosidase activity was determined in whole liver homogenates [100mg fresh tissue/ml 0.25M Tris-HCl (pH 7.3)] using the O-nitrophenyl-β-D-galactopyranoside (ONPG) assay according to standard techniques. After appropriate dilution the homogenate was incubated with β-galactosidase assay reagent (0.1M sodium phosphate buffer (pH7.3)/1mM $MgCl_2$/50 mmol β-mercaptoethanol/0.88mg/ml ONPG) at 37°C, quenched by the addition of 1M Na_2CO_3 and the absorbance at 420nm determined. The units of β-galactosidase activity are given as A_{420}/mg liver/minute.

The levels of endogenous mouse Cyp3a mRNA expression were determined by Northern analysis using a riboprobe complementary to nucleotides 852-1061 of the mouse Cyp3a11 cDNA. Filters were stripped and reprobed with an 18S rRNA oligonucleotide to normalise loading.

RESULTS

4 transgenic lines were generated with the construct containing the -3.2kb region of the human *CYP3A4* gene linked to *lacZ*. Transgene-derived β-galactosidase activity was not detected in kidney, large and small intestine, spleen, lung and liver tissue from mice for all 4 -3CYP3A4/*lacZ* transgenic lines treated with vehicle or xenobiotics (Table 1). In contrast, transgene expression was readily detected in 3 of the 4 lines carrying the -13CYP3A4/*lacZ* construct. Line 9/4 had a very low constitutive level in the liver, with β-galactosidase detected only in isolated hepatocytes adjacent to major blood vessels. Administration of xenobiotics resulted in robust expression in a zone of cells surrounding the central vein (Figure 2). As the basal level of transgene expression in untreated mice in line 9/4 is extremely low, induction is obvious and is essentially an off/on process. Expression in other tissues in mice from line 9/4 was restricted to the gut, predominantly in the villi of the small intestine.

The relative degree of induction for a range of xenobiotics was analysed by determining the transgenic β-galactosidase activity in liver lysates of mice from line 9/4 (Figure 3A). Dexamethasone and pregnenolone 16α-carbonitrile were the most potent inducers, while rifampicin activated the transgene to relatively modest levels. Phenobarbital, clotrimazole and phenytoin were intermediate inducers. The induction profile of the transgene in line 9/4 was similar to that observed for the endogenous *Cyp3a11* gene in the same mice (Fig 3B), likely reflecting the activation profile of the mouse rather than the human PXR. Activation of the transgene was observed with naturally occurring

steroids such as pregnenolone and 17α-progesterone, however the induction was weak compared with xenobiotics.

There was a marked gender difference in hepatic transgene expression, with lower levels observed in females than in males for most reagents. Such a male-predominant pattern was not evident in the induction profile of the mouse *Cyp3a11* gene. Indeed higher levels of Cyp3a11 mRNA were observed in females than males after treatment with rifampicin and pregnenolone 16α-carbonitrile. The reason for this apparent reversal in gender-related transgene expression pattern is not known. However, as Cyp3a11 mRNA is only just detectable in males of the FVB/N strain of mice, it may be attributed to the relatively greater degree of induction of the mouse *Cyp3a11* gene in males compared to females (Figure 3B).

The other line which showed significant transgene expression - 15/10, had a higher constitutive level in both the liver and small intestine in untreated mice.

Expression was not detected in other organs, confirming the tissue specificity observed in line 9/4. The same set of reagents were capable of increasing hepatic and intestinal transgene expression to the same levels as in mice from line 9/4. However, the overall degree of induction was not as great as observed in line 9/4 due to the higher basal level in line 15/10. The induction profile was similar with dexamethasone being the most potent activator and rifampicin the least (data not shown).

Dose response of xenobiotic induction. The activation of transgene expression in line 9/4 by dexamethasone was dose-dependent over the range 1 to 100 mg/kg (Figure 4A). The higher transgene-derived β-galactosidase activity in liver homogenates from mice treated with increasing doses of

dexamethasone was associated with an expanded zone of cells which were stained by X-gal. At low doses of dexamethasone a ring of hepatocytes only 1-2 cells thick around the central vein expressed the transgene (Figure 4B). With 100mg/kg dexamethasone the zone of X-gal positive hepatocytes increased to up to 10 cells, approximately midway between the central vein and the portal triad. A similar dose-dependent expansion of hepatocytes expressing the transgene was observed with other reagents and also in line 15/10 which also contained the -13CYP3A4/lacZ construct.

CLAIMS

1. A non-human mammal comprising:
(a) a regulatory nucleic acid molecule which is capable of regulating transcription of the human CYP3A4 gene and which comprises a nucleotide sequence that is identical to a sequence of the human CYP3A4 gene located between the initiation of transcription site of the gene and a position located at least 13,000 nucleotides upstream from the site; and
(b) a reporter nucleic acid molecule for producing a detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule;
wherein the reporter and regulatory nucleic acid molecules are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

2. A non human mammal comprising:
(a) a regulatory nucleic acid molecule comprising a nucleotide sequence that is identical to the nucleotide sequence of the human CYP3A4 gene that extends about 13,000 nucleotides upstream from the initiation of transcription site of the gene; and
(b) a reporter nucleic acid molecule for producing a detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule;
wherein the reporter and regulatory nucleic acid molecules are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

3. A mammal according to claim 2 wherein the regulatory nucleic acid molecule comprises the sequence shown in SEQ ID NO:1.

4. A non-human mammal comprising:
(a) a regulatory nucleic acid molecule comprising a nucleotide sequence that is identical to the sequence of the human CYP3A4 gene that extends about 8,000 nucleotides upstream from a position about 3,000 nucleotides upstream from the initiation of transcription site of the gene; and
(b) a reporter nucleic acid molecule for producing a detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule;
wherein the reporter and regulatory nucleic acid molecules are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

5. A mammal according to claim 4 wherein the regulatory nucleic acid molecule comprises the sequence shown SEQ ID NO:2.

6. A non-human mammal comprising:
(a) a regulatory nucleic acid molecule which is capable of regulating transcription of the human CYP3A4 gene and which comprises a nucleotide sequence that is identical to the sequence of the human CYP3A4 gene that extends about 600 nucleotides upstream from a position about 7,200 nucleotides upstream of the initiation of transcription site of the gene; and
(b) a reporter nucleic acid molecule for producing a detectable amount of a reporter molecule for indicating regulation of transcription of the reporter nucleic acid molecule by the regulatory nucleic acid molecule;
wherein the reporter and regulatory nucleic acid molecules are arranged to permit the regulatory nucleic acid molecule to regulate transcription of the reporter nucleic acid molecule.

7. A mammal according to claim 6 wherein the regulatory nucleic acid molecule comprises the sequence shown in SEQ ID NO:3.

8. A mammal according to any one of the preceding claims wherein the regulatory nucleic acid molecule has the sequence of a fragment of the CYP3A4 gene consisting of from nucleotide positions −7836 to −7207 contiguous with −362 to +53.

9. A mammal according to any one of the preceding claims, further comprising:

(c) a further regulatory nucleic acid molecule which is capable of regulating transcription of a human gene; and

(d) a further reporter nucleic acid molecule for producing a detectable amount of a further reporter molecule for indicating regulation of transcription of the further reporter nucleic acid molecule by the further regulatory nucleic acid molecule;

wherein the further reporter and further regulatory nucleic acid molecules are arranged to permit the further regulatory nucleic acid molecule to regulate transcription of the further reporter nucleic acid molecule.

10. A mammal according to claim 9 wherein the at least one further regulatory nucleic acid molecule has a sequence shown in SEQ ID NO:4.

11. A mammal according to claim 9 wherein the at least one further regulatory nucleic acid molecule has a sequence shown in SEQ ID NO:5.

12. A mammal according to any one of the preceding claims, further comprising at least one human transcription factor for regulating transcription of a human CYP3A4 gene.

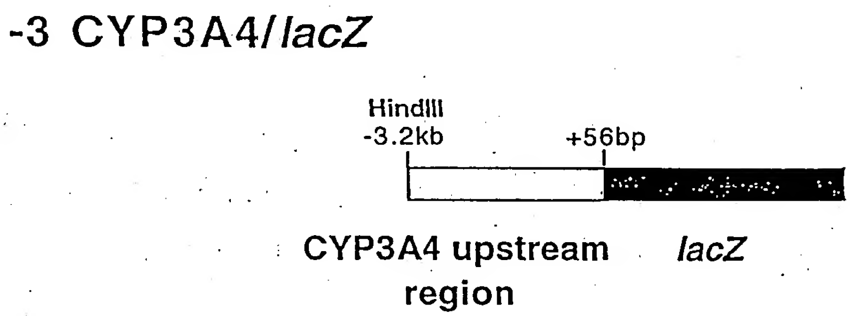
13. A mammal according to claim 12 wherein the transcription factor is a nuclear receptor.

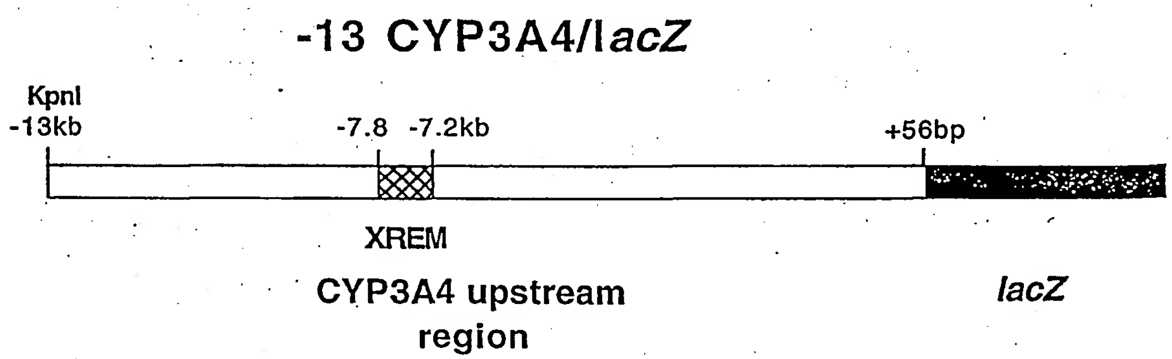
14. A mammal according to claim 13 wherein the nuclear receptor is a heterodimer of the human pregnane X receptor and human 9-cis retinoic acid receptor or a heterodimer of human constitutive androstane receptor-β and human 9-cis retinoic acid receptor..
15. A mammal according to any one of the preceding claims wherein the reporter nucleic acid molecule is capable of producing a reporter molecule selected from the group of reporter molecules consisting of firefly luciferase, β-galactosidase, alkaline phosphatase, green fluorescent protein or chloramphenicol acetyl transferase.
16. A mammal according to any one of the preceding claims wherein the mammal is a mouse.
17. A tissue of a mammal according to any one of the preceding claims.
18. A tissue according to claim 17 wherein the tissue is an embryo capable of producing a mammal according to any one of the preceding claims.
19. A method of determining whether a compound is capable of effecting the transcription of a human CYP3A4 gene the method comprising the following steps:
   (a) administering the compound to a non human mammal according to any one of the preceding claims; and
   (b) determining whether the reporter molecule is produced by the reporter nucleic acid molecule in the mammal.
20. A method according to claim 19 wherein the production of the reporter molecule indicates that the binding compound is capable of effecting the transcription of the human CYP3A4 gene.

Table 1. Expression of CYP3A4/*lacZ* transgenic lines

Construct	Line No.	Copy No.	LIVER		Small Intestine
			Basal	Inducible	
-3CYP3A4/ lacZ	13	15	-	-	-
	24	>100	-	-	-
	31	80	-	-	-
	39	10	-	-	-
-13CYP3A4/ lacZ	13/5	70	-	-	
	9/4	5	+	++++	+
	9/7	50	-	+	-
	15/10	8	++	++++	++++

Fig 1. Human CYP3A4/*lacZ* transgene constructs





Pregnenolone-16α carbonitrile | Phenobarbital | Rifampicin | Control

Figure 2. Xenobiotic induction of CYP3A4/lacZ transgene

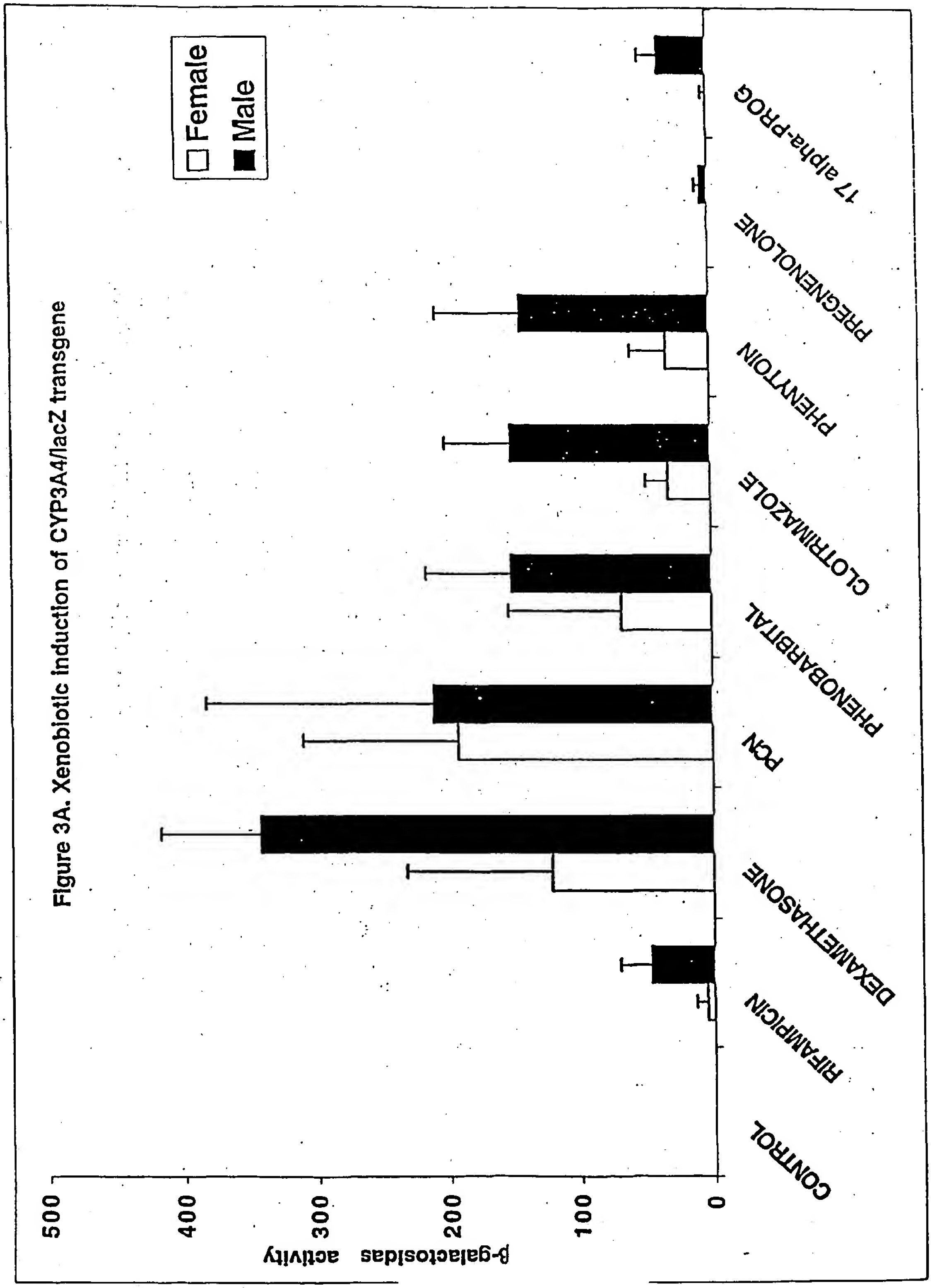


Figure 3A. Xenobiotic induction of CYP3A4/lacZ transgene

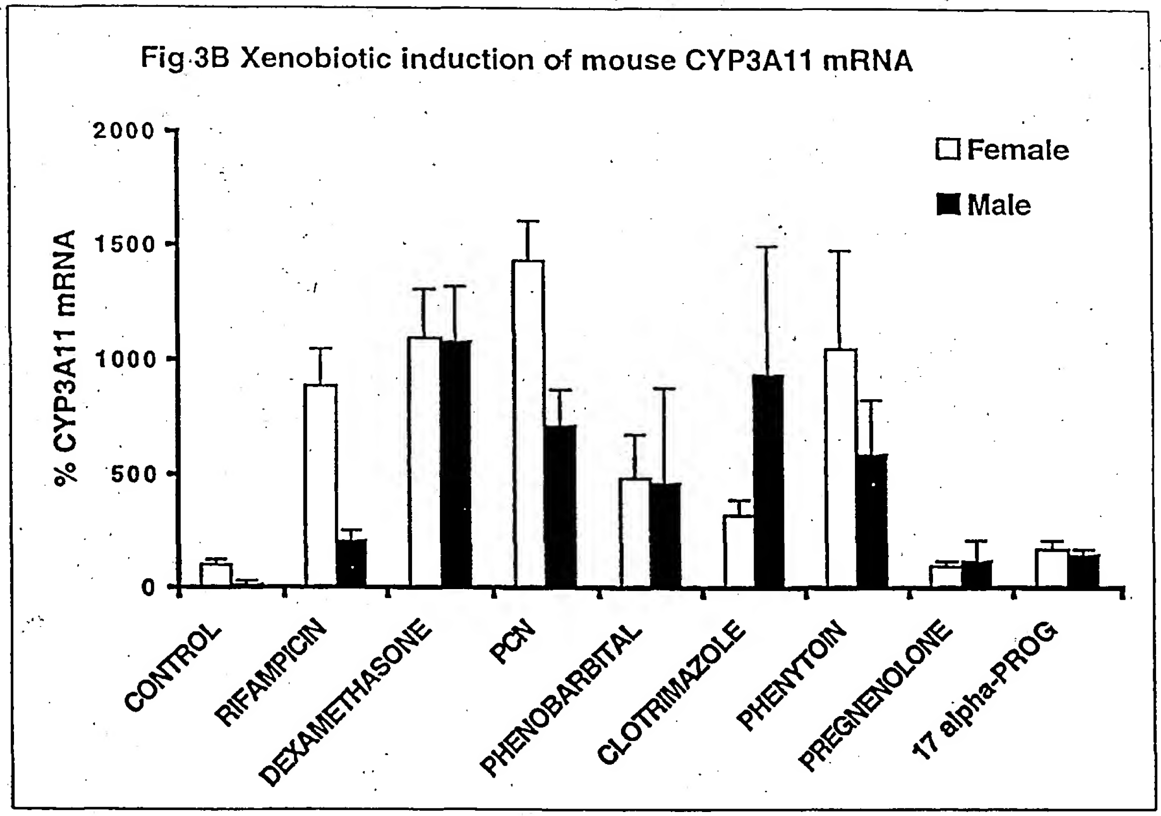


Fig 3B Xenobiotic induction of mouse CYP3A11 mRNA
2000
1500
1000
500
0
% CYP3A11 mRNA
Female
Male
CONTROL
RIFAMPICIN
DEXAMETHASONE
PCN
PHENOBARBITAL
CLOTRIMAZOLE
PHENYTOIN
PREGNENOLONE
17 alpha-PROG

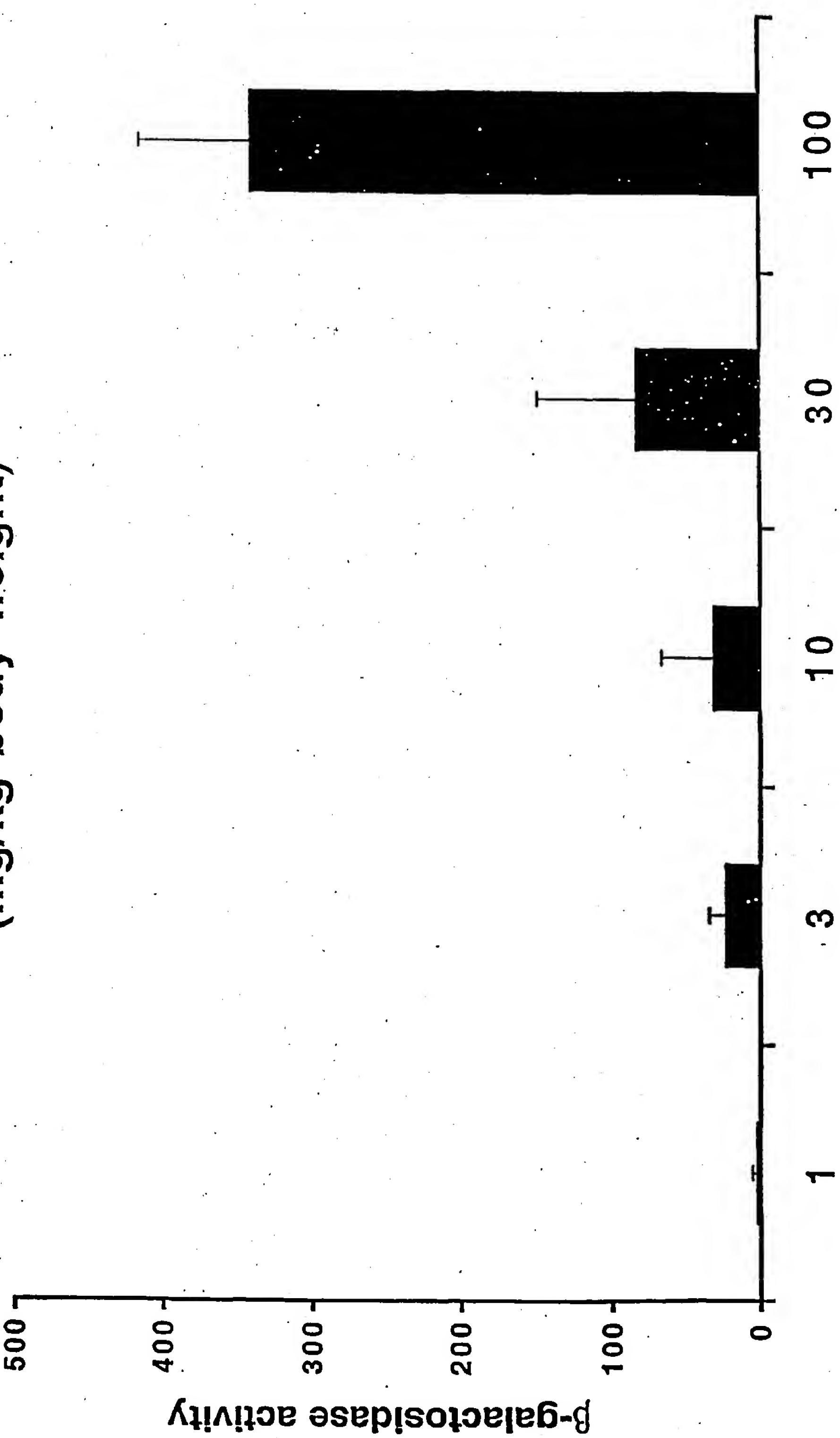
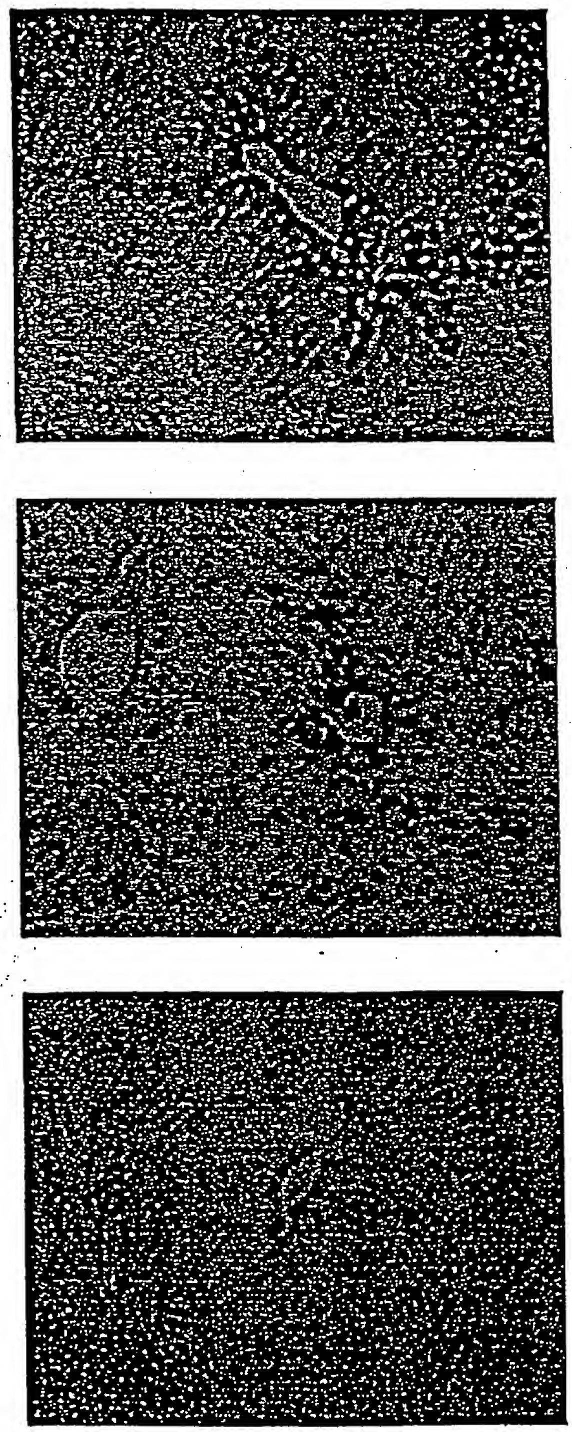


Figure 4A Dexamethasone dose-response
(mg/kg body weight)



100 mg/kg

10 mg/kg

1 mg/kg

Figure 4B. Dose response of transgene expression

Figure 5.

CTGGTTCATCTCATTGGGACTGGTTGGACAAGAGGGTGCAGCCCACGGAGGGTGAGCCAAAGCAGGGTGGG
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GAATCACTGCTGTGCAGGGCAGGAAAGCTCCATGCACATAGCCCAGCAAAGAGCAACACAG

Figure 6.

CTGGTTCATCTCATTGGGACTGGTTGGACAAGAGGGTGCAGCCCACGGAGGGTGAGCCAAAGCAGGGTGGG
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AAAGAAAATGTGGCACATATACACTGTGGAATACTATGCAGCCATAAAAAAGGATGAGTTCATGTCCTTTG
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TGCCTTCTCCAATGCTCCCTTCCGTAGGTCACTCTGTGGCTCAGAGACCCTGCTTAGCAAGCGCCCAACCT
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CTTTTTTTTTTTTGGTTTACATCCTCAAGATCATGACTTGTGAAATTTGAATCGAATACACATGTAATTC
CAGAGCAATGTTGCCTCCGCATACCATCAGCAATTCACTTGGCTACTGGAAGTCAGGAT

Figure 7.

TCTAGAGAGA TGGTTCATTC CTTTCATTTG ATTATCAAAG AAACTCATGT CCCAATTAAA
GGTCATAAAG CCCAGTTTGT AAACTGAGAT GATCTCAGCT GAATGAACTT GCTGACCCTC
TGCTTTCCTC CAGCCTCTCG GTGCCCTTGA AATCATGTCG GTTCAAGCAG CCTCATGAGG
CATTACAAAG TTTAATTATT TCAGTGATTA TTAAACCTTG TCCTGTGTTG ACCCCAGGTG
AATCACAAGC TGAACTTCTG ACAAGAACAA GCTATCATAT TCTTTTCAAT TACAGAAAAA
AGTAAGTTAA TTGATAGGAT TTTTTTTGTT TAAAAAAAAT GTTACTAGTT TTTGAAAAGG
TAATATGTTG CACATGGTAA ACACTAAGAA GGTATAAGAG CATAATGCTT TTATACTACT
AAGAATAATG TTTTCTCTAA GTTTTTTTTG GTAGATGCTT TCATCAGATT AAGAAAATTC
CCTGCTATTA GTTGTTGAAG GTTTTTATAT CATAAATGAA AGTTGAATAT TATTATCATA
TATTATTAAT ATATTGTTAT TGAACTATCA AAGCCTTTTC CTAAAACCAT TGAGATGATC
TTATAACCAT TCTCCTTTAA CCTGTTGACG AG

Figure 8.

GGATCCAGTTTCAGCTTTCTACATATGGCTAGCCAGTTTTCCCAGCACCATTTATTAAATAGGGAATCCTT
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Figure 9.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01407

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. 7: C12N 15/63, 5/10, C12Q 1/68, A01K 67/027, A61K 49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ELECTRONIC DATABASE BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEE ELECTRONIC DATABASE BELOW

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Medline, WPIDS, CAPlus. Keywords: CYP3A4, silencer, enhancer, promoter, regulator, regulate, regulating, regulon.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/48915, A (GLAXO GROUP LIMITED) 30 September 1999. See page 17 lines 13-18.	1-20
Y	Eur J Drug Metab Pharmacokinet (1997) 22(4):311-3. Ogg MS, Gray TJB, Gibson GG. "Development of an in vitro reporter gene assay to assess xenobiotic induction of the human CYP3A4 gene." See whole document.	1-20
	Note: for the Y indications, WO 99/48915 and Eur J Drug Metab Pharmacokinet (1997) can be combined together.	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2001	24 DEC 2001
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **J.H. CHAN** Telephone No : (02) 6283 2340

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01407

C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Cancer Chemother Pharmacol (1998) 42 Suppl:S50-3. Kamataki T, Yokoi T, Fujita K, Ando Y. "Preclinical approach for identifying drug interactions." See whole document.	
A	Chem Biol Interact (1997) 107(1-2):93-108. Olsen AK, Hansen KT, Friis C. "Pig hepatocytes as an in vitro model to study the regulation of human CYP3A4: prediction of drug-drug interactions with 17 alpha-ethynylestradiol." See whole document.	
A	WO 99/61622, A (THE UNIVERSITY OF SYDNEY) 2 December 1999. See whole document.	

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/01407

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
WO	9961622	AU	40232/99	EP	1082437
WO	9948915	AU	32116/99	EP	1066320

END OF ANNEX